REMARKS

I.   Status of the Claims

Claims 1-15 and 29-31 are pending and under consideration. Claims 16-28 and 32 were previously cancelled without prejudice or disclaimer. No claims are being amended in this Reply.

II.   Double Patenting Rejection

The Office provisionally rejects claims 1-15 and 26-31 on the ground of nonstatutory obviousness-type double patenting as allegedly "being unpatentable over claims 1, 3-7 of copending Application No. 10/540,123" to Göhl et al. ("*Göhl*"). Office Action, page 2.

Applicants respectfully disagree. However, Applicants request that the Examiner hold the rejection in abeyance until an indication of otherwise allowable subject matter has been made. Moreover, Applicants respectfully point out that the filing date of the present application is June 17, 2005, which is prior to the filing date of *Göhl* of June 20, 2005. Thus, "if 'provisional' [obviousness-type double patenting] rejections in two applications are the only rejections remaining in those applications, the Office should withdraw the [obviousness-type double patenting] rejection in the earlier filed application thereby permitting that application to issue without need of a terminal disclaimer."
M.P.E.P. § 804 I.B.1.

III.   Rejections under 35 U.S.C. § 102 or § 103

A.   *Buck* as evidenced by *Gorsuch*

The Office rejects claims 1, 7-11, 13, and 26-29 under 35 U.S.C. § 102(b) as allegedly anticipated by, or in the alternative, under 35 U.S.C. § 103(a), as allegedly obvious over U.S. Patent No. 4,935,141 to Buck et al. ("*Buck*") as evidenced by U.S. Patent No. 6,802,820 to Gorsuch et al. ("*Gorsuch*"). Office Action, pages 2-4. The Office further stated that Applicant's arguments filed on July 10, 2009, have been fully considered but not found persuasive in view of the new grounds of rejection. *Id.* at page 14.

Applicants respectfully traverse and submit that the rejected claims are neither anticipated by *Buck* nor obvious over the combination of *Buck* and *Gorsuch* for the reasons outlined below.

1.   *Buck* does not anticipate the rejected claims at least because *Buck* does not disclose the limitation of a membrane having a "molecular weight exclusion limit of about 200,000 Daltons, with a sieving coefficient of 0.1 in water," neither explicitly nor inherently

Applicants respectfully remind the Office that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987).

The Office has not shown that *Buck* meets this requirement. Instant claim 1 recites (emphasis added):

> A permselective asymmetric hollow fibre membrane for the separation of toxic mediators from blood, comprised of at least one hydrophobic polymer and at least one hydrophilic polymer, wherein said membrane **allows passage of**

> molecules having a molecular weight of up to 45 000
> Daltons, with a sieving coefficient of 0.1-1.0 in presence
> of whole blood, and has a molecular weight exclusion
> limit of about 200,000 Daltons, with a sieving coefficient
> of 0.1 in water.

Central to the Office's position is the allegation that"[i]t is *inherent* that the hollow

fiber membrane has a molecular weight exclusion limit in water of about 200 kDa."

Office Action, page 3 (emphasis added). Applicants respectfully submit that this

allegation is based on an incomplete or incorrect reading of *Buck*.

In fact, *Buck* expressly states that the membrane according to its invention has

an exclusion limit of the size of albumin or smaller:

> [I]n accordance with the present invention, the applicants
> have provided a selectively permeable asymmetric
> membrane [...] **the substantially uniform pore openings
> in the first layer having a size whereby proteins which
> have a molecular weight of at least that of albumin are
> substantially completely rejected** from the membrane.

Buck at col. 1, line 67, to col. 2, line 16 (emphasis added). Since albumin has a

molecular weight of 68 kDa (see *Buck* at col. 5, line 39), *Buck*'s membrane therefore

has an exclusion limit of less than 68 kDa. Although this particular passage is silent as

to whether the exclusion limit of less than 68 KDa is measured in water or in whole

blood, it can be easily seen from *Buck's* Figure 3 that *Buck's* membrane excludes at

least molecules having a higher molecular weight than 68 KDa in *both* water and

bloodin *both* water and blood. That is, the exclusion limit of less than 68 KDa is for *both*

water and blood. This clearly shows that *Buck's* membrane does not have "a molecular

weight exclusion limit of about 200,000 Daltons, with a sieving coefficient of 0.1 in

water," as instantly recited.

Applicants note that the drawing sheet containing Figures 3 and 4 is missing from *Buck* (U.S. Patent No. 4,935,141) as it is available from the website of the U.S. Patent and Trademark Office. However, Figures 3 and 4 are discussed in *Buck's* specification and these figures are part of European Application No. EP 0 305 787, which is the European member of *Buck's* patent family. EP 0 305 787 claims priority from *Buck's* Swedish priority Application No. 0203855-2, which also contains the same Figures 3 and 4. Applicants enclose a copy of the drawing sheet containing Figures 3 and 4 missing from the U.S. patent but available from *Buck's* European application. EP 0 305 787 is also listed in an Information Disclosure Statement filed concurrently herewith. Figure 3 is a graph of the sieving coefficients of membranes including membranes according to *Buck's* invention. *Buck* at col. 3, lines 28-30. The membranes according to *Buck's* invention (labeled "PA without PVP" in Figure 3) show only a small difference between sieving coefficients measured in water (in vitro) or in plasma or whole blood (in vivo). *Buck* at col. 6, lines 3-6, and Figure 3. Figure 3 also shows membranes of the art (labeled "PA with PVP" in Figure 3) for comparative purposes. *Buck* at col. 6, lines 7-11, and Figure 3. It is easily evident from the graphs in Figure 3 that the sieving coefficients of *Buck's* membranes are below 0.1 and close to zero for molecules of the size of albumin in *both* water and blood. Since the molecular weight of a substance having a sieving coefficient of 0.1 or less in water is at or below the exclusion limit of a membrane (see, e.g., the instant specification at page 8, lines 27-35), Figure 3 therefore corroborates that albumin, with a size of 68 kDa, is above the exclusion limit of *Buck's* membranes in *both* water and blood.

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Again, a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. Consequently, *Buck* **cannot** anticipate the claims, because the element of "molecular weight exclusion limit of about 200,000 Daltons, with a sieving coefficient of 0.1 in water" as set forth in claim 1 is not disclosed, expressly or inherently, in *Buck*.

> **2.   The Office has failed to make a *prima facie* case of obviousness because it has failed to show that one of ordinary skill in the art would have combined the references as proposed**

The Office argues that "it has been held obvious to optimize result effective variable (size exclusion limits and sieving coefficients) and Buck discloses that size exclusion limits are result-effective variables in filtration (C5/L1-56)." Office Action at 3. Based on this allegation, the Office concludes that the invention "would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made." *Id.* at 4. Applicants respectfully traverse this rejection, at least because, as will be shown below, *Buck* teaches against the optimization of size exclusion limits above a value of 68 KDa .

In particular, in the instant case, at least three reasons require a conclusion that the invention was non-obvious at the time of filing. First, the prior art teaches away from the instant invention. Second, there was no suggestion in the art for one of ordinary skill in the art to pursue the combination of the cited references suggested by the Office. And third, one of ordinary skill in the art would have had no reasonable expectation of success in arriving at the claimed invention.

a.   **The prior art teaches away from the instant invention (e.g., exclusion limit of 200 kD in water) because it suggests membranes having an exclusion limit of less than 68 kD in both water and blood**

Buck teaches that the membranes of its invention comprise a hydrophobic polymer and hydrophilic polymer and that they have an integral three-layered structure with an exclusion limit of less than 68 KDa in both water and blood.

As discussed above, Figure 3 in *Buck* demonstrates membranes with sieving coefficients of much less than 0.1 in *both* water and blood for molecules having a molecular weight approximately that of albumin (*i.e.*, 68 KDa). *Buck* explains that the exclusion limit of less than 68 kD is ***required*** for membranes intended for hemodialysis or hemofiltration:

> Membranes which are intended for use in hemodialyis and hemofiltration on one hand required the above-described high permeability, while on the other hand ***they must also reject proteins with high molecular weight. For albumin (M_w 68,000) the rejection should be infinite or close to infinite***.

Buck at col. 5, lines 34-39 (emphasis added). *Buck* further teaches that it is ***an advantage*** if the difference between a membrane's sieving coefficients in water (in vitro) and in plasma or whole blood (in vivo), respectively, is *smaller*, rather than *larger*:

> Another ***advantage*** of the membranes according to the present invention is that ***the difference between the sieving coefficients, measured in water (in vitro) and in plasma or whole blood (in vivo), respectively, is <u>small</u>***. Once again referring to FIG. 3, there is also shown therein for comparative purposes the sieving coefficient of a membrane made from the same hydrophobic PA (polyamide) material, but without the addition of the hydrophilic polymer. In that membrane there is shown to be a significantly large difference between "in vitro" and "in vivo" sieving.

Buck at col. 6, lines 3-13 (emphasis added). *Buck*, therefore, teaches that its membranes must have an exclusion limit of less than 68 kD, corresponding to a sieving coefficient of 0.1 or less for molecules with a molecular weight of 68 kD, and that it is advantageous for such membranes to have a smaller, rather than a larger, difference between its sieving coefficient in water and in whole blood, which clearly advises against the "optimization" of size exclusion limits proposed by the Office. **This analysis clearly shows, contrary to the main argument by the Office, that it is not *inherent* for a membrane that has an exclusion limit of 68 KDa in whole blood to have an exclusion limit of 200 KDa in water.**

The difference in the measurements of the sieving coefficients in water and in blood for the instant membrane is different from that in *Buck*. *See e.g.,* Figure 3 of the instant application. Figure 3 illustrates that the instant membrane has a sieving coefficient of approximately 0 for a 150kD molecule in whole blood, therefore excluding most, if not all of the 150kD molecule in blood. However, the same 150kD molecule passes through at approximately 100% in water. Such a large difference between blood and water sieving coefficients for the instant membrane is not taught or suggested in any embodiment of *Buck*.

Given the suggestion in *Buck* that the membrane have an exclusion limit of less than 0.1 for molecules having a molecular weight of 68 kD in both blood and water, and the explicit teaching against increasing the difference in sieving coefficients in water and whole blood, one of ordinary skill in the art would not have been led to prepare a membrane according to the invention, which recites, *inter alia*, an "exclusion limit of about 200 kD," a "sieving coefficient of 0.1 in water," and a "sieving coefficient of 0.1-1.0

in presence of whole blood." Thus, a person of ordinary skill, upon reading *Buck*, would undoubtedly be led in a direction divergent from the instantly recited membrane.

A prior art reference that teaches away from the claimed invention and proceeding contrary to accepted knowledge in the art are evidence of non-obviousness. M.P.E.P § 2145(X)(D). Therefore the instant claims are non-obvious in light of *Buck*'s teachings. Accordingly, for at least this reason, Applicants respectfully request that this rejection be withdrawn.

Gorsuch provides nothing that would change this conclusion, and was only cited as alleged evidence of the properties of *Buck's* membranes. As explained in Applicants response filed July 10, 2009, *Gorsuch's* disclosure is not relevant to the properties of *Buck's* membranes. In fact, *Gorsuch* confirms that the prior art teaches that a membrane intended for hemofiltration should have an exclusion limit of less than 68 kD. Curve 11 in Figure 7 shows a "typical sieving coefficient curve" for membranes used for hemofiltration. *Gorsuch* at col. 3, line 57, to col. 4, line 11. Curve 11 shows that a protein of 68 kD has a sieving coefficient below 0.1, and hence, according to *Gorsuch*, a typical membrane used for hemofiltration has an exclusion limit of less than 68 kD. This is, therefore, further **proof that the Office's assertion that figure 7 of *Gorsuch* provides "evidence" that *Buck's* membranes have an exclusion limit in water of 200kD is incorrect.**

The Office asserts that Gorsuch "provides evidence in Fig. 7 that size exclusion limits and sieving coefficients can be easily manipulated based on the test methods used to determine the size exclusion limits and sieving coefficients....Therefore, many hollow fiber membranes would appear to have the desired size exclusion limit and

sieving coefficients." Office Action, page 3. The Office concludes that "the size

exclusion limit and sieving coefficient has no limiting effect." *Id.* Aside from the fact that

the Office has provided no explanation of which "test methods" it is referring to,

Applicants respectfully disagree. Contrary to the Office's assertion, Figure 7 says

nothing about easy manipulation of exclusion limits and sieving coefficients based on

test methods. Rather, as mentioned above, Figure 7 shows typical sieving coefficient

curves for hemofiltration, which show that such a membrane has an exclusion limit of

less than 68 kD.

> **b.** **There was no suggestion in the art for one of ordinary skill in the art to pursue the combination of the cited references suggested by the Office**

One of ordinary skill in the art would have had no suggestion to pursue the

proposed combination suggested by the Office for at least the following reason. *Buck*

teaches away from using a membrane with an exclusion limit of higher than 68 kD, in

both water and blood, and from increasing the difference between the membrane's

sieving coefficient in water and in whole blood, respectively. Nothing in *Gorsuch*

overcomes or contradicts *Buck*'s teaching away or otherwise points one of skill in the art

in the direction of any new invention, much less the instant invention.

For this independent reason, Applicants respectfully request that this rejection be

withdrawn.

c. There was no reasonable expectation of success in arriving at the claimed invention

One of ordinary skill in the art had no reasonable expectation of success in arriving at the claimed invention based on *Buck* and *Gorsuch* for the reasons presented in the previous sections.

~~In brief, *Buck* teaches away from using a membrane with an exclusion limit of~~ higher than 68 kD, in *both* water and blood, and from increasing the difference between the membrane's sieving coefficient in water and in whole blood, respectively. Nothing in *Gorsuch* overcomes or contradicts *Buck*'s teaching away or otherwise suggests that a membrane according to the instant invention may be successfully used in hemodialysis or hemofiltration.

Accordingly, Applicants respectfully submit that the Office has failed to establish a *prima facie* case of obviousness, because one skilled in the art would not have had a reasonable expectation of success based on *Buck* and *Gorsuch*.

<u>In summary</u>, Applicants respectfully submit that claims 1, 7-11, 13, and 26-29 are neither anticipated by *Buck* nor obvious over *Buck* and *Gorsuch* for at least the independent reasons outlined above. Thus, Applicants request that the rejections under 35 U.S.C. § 102(b), or in the alternative, under 35 U.S.C. § 103(a), based on *Buck* and *Gorsuch* be withdrawn.

B. *Kawata* as evidenced by *Gorsuch*

The Office rejects claims 1, 3-11, 13-14, 26-29, and 30 under 35 U.S.C. § 102(b) as anticipated by, or, in the alternative, under 35 U.S.C. § 103(a), as allegedly being

obvious over EP 0 568 045 to Kawata et al. ("*Kawata*")[1] as evidenced by *Gorsuch*.

Office Action, pages 4-7. The Office further stated that Applicant's arguments filed on

July 10, 2009, have been fully considered but not found persuasive in view of the new

grounds of rejection. *Id.* at page 14.

Applicants respectfully traverse and submit that the rejected claims are neither

anticipated by *Kawata* nor obvious over the combination of *Kawata* and *Gorsuch*, for the

reasons outlined below.

1.   *Kawata* does not anticipate the rejected claims because *Kawata* does not disclose the limitation of a membrane having a "molecular weight exclusion limit of about 200,000 Daltons, with a sieving coefficient of 0.1 in water," neither explicitly nor inherently

Central to the Office's position is the allegation that"[i]t is ***inherent*** that the hollow

fiber membrane has a molecular weight exclusion limit in water of about 200 kDa and

sieving coefficient of 0.1-1.0 in the presence of blood and sieving coefficient of 0.1 in

water, as evidence by Gorsuch (Fig.7)." Office Action, page 5 (emphasis added).

Applicants respectfully submit that this allegation is based on an incorrect reading of

Kawata and that it is not necessary to resort to *Gorsuch* to determine the exclusion

limits of *Kawata's* membranes. *Kawata* expressly teaches in Example 7 that the

membranes according to its invention have a sieving coefficient of albumin of less than

0.1. *Kawata* at page 15, line 10, to page 16, line 6; *see* Table 1. Table 1 shows that all

of the tested membranes according to *Kawata's* invention have a sieving coefficient of

albumin of about 0.001. Since albumin has a molecular weight of 68 kDa (see, e.g.,

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[1] Applicants note that the Office refers to Kagawa as the first named inventor for EP 0 568 045.
However, Kawata is the first named inventor listed on EP 0 568 045, and Applicants will
therefore refer herein to EP 0 568 045 as "*Kawata*."

Buck at col. 5, line 39), *Kawata*'s membranes therefore have an exclusion limit of less than 68 kDa. The Office has cited no evidence suggesting that *Kawata's* membranes allow passage of molecules having a molecular weight of up to 45 000 Daltons, with a sieving coefficient of 0.1-1.0 in presence of whole blood, and has a molecular weight exclusion limit of about 200,000 Daltons, with a sieving coefficient of 0.1 in water as instantly recited.

Gorsuch provides nothing that would change this conclusion. In fact, *Gorsuch* confirms that the prior art teaches that a membrane intended for hemofiltration should have an exclusion limit of less than 68 kD. Curve 11 in Figure 7 shows a "typical sieving coefficient curve" for membranes used for hemofiltration. *Gorsuch* at col. 3, line 57, to col. 4, line 11. As mentioned before, Curve 11 shows that a protein of 68 kD has a sieving coefficient below 0.1, and hence, according to *Gorsuch*, a typical membrane used for hemofiltration has an exclusion limit of less than 68 kD. This is, therefore, further **proof that the Office's assertion that figure 7 of *Gorsuch* provides "evidence" that *Kawata* membranes have an exclusion limit in water of 200kD is incorrect.**

In summary, *Kawata* cannot anticipate the claims at least because the recitation regarding the membrane allowing passage of molecules having a molecular weight of up to 45 000 Daltons, with a sieving coefficient of 0.1-1.0 in presence of whole blood, and has a molecular weight exclusion limit of about 200,000 Daltons, with a sieving coefficient of 0.1 in water not disclosed, expressly or inherently, in *Kawata*.

2. **The Office has failed to make a *prima facie* case of obviousness because it has failed to show that one of ordinary skill in the art would have combined the references as proposed**

In the instant case, at least three reasons each separately or in combination require a conclusion that the invention was non-obvious at the time of filing. First, the prior art teaches away from the instant invention. Second, there was no suggestion in the art for one of ordinary skill in the art to pursue the combination of prior art reference teachings suggested by the Office. And third, one of ordinary skill in the art had no reasonable expectation of success in arriving at the claimed invention.

a. **The prior art teaches away from the instant invention**

As mentioned above, the prior art, exemplified in this case by the teachings and disclosure of *Buck, Gorsuch*, and *Deppisch* (see section below addressing the rejection based on *Deppisch*), teaches away from preparing membranes having an exclusion limit greater than 68 kD in water. *Kawata's* disclosure show that its membranes also have an exclusion limit greater than 68 kD. The Office has provided no evidence that one of ordinary skill in the art wanting to prepare membranes for hemodialyis and hemofiltration would be led to "optimize" the exclusion limit to arrive to a membrane that allows passage of molecules having a molecular weight of up to 45 000 Daltons, with a sieving coefficient of 0.1-1.0 *in presence of whole blood*, and has a molecular weight exclusion limit of about 200,000 Daltons, with a sieving coefficient of 0.1 *in water*.

Thus, at least because the art teaches away from the invention, Applicants respectfully request that this rejection be withdrawn.

b.   There was no suggestion in the art for one of ordinary skill in the art to pursue the combination of prior art reference teachings suggested by the Office

One of ordinary skill in the art had no good reason nor guidance to pursue the proposed combination suggested by the Office for at least the following reason. *Kawata* teaches a membrane with an exclusion limit of less than 68 kD. *Kawata* at page 15, line 10, to page 16, line 6. Nothing in *Kawata* suggests a membrane that allows passage of molecules having a molecular weight of up to 45 000 Daltons, with a sieving coefficient of 0.1-1.0 *in presence of whole blood*, and has a molecular weight exclusion limit of about 200,000 Daltons, with a sieving coefficient of 0.1 *in water*. And nothing in *Gorsuch* overcomes this limitation or otherwise points one of skill in the art in the direction of any new invention, much less the instant invention.

For this independent reason, Applicants respectfully request that this rejection be withdrawn.

c.   There was no reasonable expectation of success in arriving at the claimed invention

One of ordinary skill in the art had no reasonable expectation of success in arriving at the claimed invention based on *Kawata* and *Gorsuch* for the reasons presented in the previous sections.

In brief, the prior art (e.g. *Buck*) teaches away from using a membrane with an exclusion limit of higher than 68 kD in hemodialyis or hemofiltration and from increasing the difference between the membrane's sieving coefficient in water and in whole blood, respectively. Nothing in *Kawata* or *Gorsuch* overcomes or contradicts *Buck*'s teaching

away or otherwise suggests that a membrane according to the instant invention may be successfully used in hemodialysis or hemofiltration.

Accordingly, Applicants respectfully submit that the Office has failed to establish a *prima facie* case of obviousness, because one skilled in the art would not have had a reasonable expectation of success based on *Kawata* and *Gorsuch*.

In summary, Applicants respectfully submit that claims 1, 3-11, 13-14, 26-29, and 30 are neither anticipated by *Kawata* nor obvious over *Kawata* and *Gorsuch* for at least the independent reasons outlined in sections B.1. and B.2. above. Thus, Applicants request that the rejections under 35 U.S.C. § 102(b), or in the alternative, under 35 U.S.C. § 103(a), based on *Kawata* and *Gorsuch* be withdrawn.

C.   Gorsuch

The Office rejects claims 1, 5-7, and 26-28 under 35 U.S.C. § 102(e) as anticipated by, or, in the alternative, under 35 U.S.C. § 103(a), as allegedly being obvious over *Gorsuch*. Office Action, pages 7-8. The Office further stated that Applicant's arguments filed on July 10, 2009, have been fully considered but not found persuasive in view of the new grounds of rejection. *Id.* at page 14.

Applicants respectfully traverse and submit that the rejected claims are neither anticipated by *Gorsuch* nor obvious over *Gorsuch*, for the reasons already outlined in the discussion in sections A. and B. above.

1.   ***Gorsuch* does not anticipate the rejected claims because *Gorsuch*
     does not disclose each and every element of the claims**

Central to the Office's position is the allegation that"[i]t is ***inherent*** that the hollow

fiber membrane has a molecular weight exclusion limit in water of about 200 kDa."

Office Action, page 7 (emphasis added).

As abundantly made clear above, this allegation is based on an incorrect reading

of *Gorsuch*. In fact, *Gorsuch* confirms the prior art teaching (e.g. by *Buck*) that a

membrane intended for hemofiltration does not have a molecular weight exclusion limit

in water of about 200 kDa. Curve 11 in Figure 7 of *Gorsuch* shows a "typical sieving

coefficient curve" for membranes used for hemofiltration. *Gorsuch* at col. 3, line 57, to

col. 4, line 11. Curve 11 shows that a protein of 68 kD has a sieving coefficient below

0.1, and hence a typical membrane used for hemofiltration has an exclusion limit of less

than 68 kD. Clearly, this teaching fails to meet the limitation in the instant claims

regarding the membrane having "a molecular weight exclusion limit of about 200,000

Daltons in water."

Moreover, there is nothing in *Gorsuch* to suggest that the membranes according

to its invention would have a molecular weight exclusion limit of about 200 kDa, with a

sieving coefficient of 0.1 in water.

The Office asserts that "[i]t is ***inherent*** that the hollow fiber membrane [of

Gorsuch] has a molecular weight exclusion limit in water of about 200 kDa and sieving

coefficient of 0.1-1.0 in the presence of blood and sieving coefficient of 0.1 in water, as

evidence by Gorsuch (Fig.7)." Office Action, page 7 (emphasis added). The Office

further asserts that *Gorsuch* "provides evidence in Fig. 7 that size exclusion limits and

sieving coefficients can be easily manipulated based on the test methods used to determine the size exclusion limits and sieving coefficients....Therefore, many hollow fiber membranes would appear to have the desired size exclusion limit and sieving coefficients." Office Action, page 7. The Office concludes that "the size exclusion limit and sieving coefficient has no limiting effect." *Id.* Aside from the fact that the Office has provided no explanation which "test methods" it is referring to, Applicants respectfully disagree for the same reasons outlined above in Section III.A.2, which include the fact that *Gorsuch* teaches that a typical membrane used for hemofiltration has an exclusion limit of less than 68 kD and provides no suggestion to develop a membrane that allows passage of molecules having a molecular weight of up to 45 000 Daltons, with a sieving coefficient of 0.1-1.0 *in presence of whole blood*, and has a molecular weight exclusion limit of about 200,000 Daltons, with a sieving coefficient of 0.1 *in water*, as instantly recited.

Thus, *Gorsuch* **cannot** therefore anticipate the claims because the element of "molecular weight exclusion limit of about 200,000 Daltons, with a sieving coefficient of 0.1 in water" as set forth in claim 1 is not disclosed, expressly or inherently, in *Gorsuch*.

2.   **The Office has failed to make a *prima facie* case of obviousness because it has failed to show that one of ordinary skill in the art would have modified *Gorsuch* as proposed**

Applicants respectfully submit that the Office has failed to make a *prima facie* case of obviousness based on *Gorsuch* for the reasons already outlined in sections A and B above. Those arguments include the fact that *Gorsuch* teaches membranes having an exclusion limit of less than 68 kD and there is no evidence cited by the Office that one of ordinary skill in the art would have been led to prepare a membrane with a

higher exclusion limit in water, as instantly recited. As mentioned above, *the teachings in Buck clearly show that the exclusion value of 200 KDa in water is not inherent.*

In summary, Applicants therefore respectfully submit that claims 1, 5-7, and 26-28 are neither anticipated by *Gorsuch* nor obvious over *Gorsuch* for at least the independent reasons outlined in sections C.1. and C.2. above. Thus, Applicants request that the rejections under 35 U.S.C. § 102(b), or in the alternative, under 35 U.S.C. § 103(a), based on *Gorsuch* be withdrawn.

D.   *Buck* as evidenced by *Kawata* and *Gorsuch*

The Office rejects claims 14-15 and 30-31 under 35 U.S.C. § 102(b) as anticipated by *Buck*, or, in the alternative, under 35 U.S.C. § 103(a), as obvious over *Buck* as evidenced by *Kawata* and *Gorsuch*. Office Action, pages 11-12. The Office further stated that Applicant's arguments filed on July 10, 2009, have been fully considered but not found persuasive in view of the new grounds of rejection. *Id.* at page 14.

Applicants respectfully traverse and submit that the rejected claims are neither anticipated by *Buck* nor obvious over the combination of *Buck*, *Kawata* and *Gorsuch*, for the reasons already outlined in the previous sections. Applicants therefore respectfully request that the rejection under 35 U.S.C. § 102(b), or in the alternative, under 35 U.S.C. § 103(a), based on *Buck*, *Kawata* and *Gorsuch* be withdrawn.

E.   *Buck* or *Kawata* or *Gorsuch* as evidenced by *Heberlin*

The Office rejects claim 12 under 35 U.S.C. § 102(b) as anticipated by *Buck* or *Kawata* or *Gorsuch*, or, in the alternative, under 35 U.S.C. § 103(a), as obvious over

Buck or *Kawata* or *Gorsuch* as evidenced by *Herbelin*. Office Action, pages 8-11. The Office further stated that Applicant's arguments filed on July 10, 2009, have been fully considered but not found persuasive in view of the new grounds of rejection. *Id.* at page 14.

Applicants respectfully traverse and submit that the rejected claims are neither anticipated by *Buck* or *Kawata* or *Gorsuch*, nor obvious over *Buck* or *Kawata* or *Gorsuch* as evidenced by *Herbelin*, for the reasons already outlined in the discussion in previous sections, and the following additional reasons.

Herbelin studies the plasma IL-6 levels in long-term dialyzed patients, including the influence of the nature of the dialysis membrane on these levels. See, e.g., *Herbelin* at page 958, Table 3. IL-6 is protein with a molecular size of about 26 kDa. *Herbelin* at page 954, col. 2, 1st full ¶. However, *Herbelin* says nothing about sieving coefficients or the molecular exclusion limits of membranes used for hemodialysis or hemofiltration. Thus, *Herbelin* fails to remedy the deficiencies of *Buck* or *Kawata* or *Gorsuch*. Accordingly, the Office has failed to establish a *prima facie* case of obviousness over the combination of any of *Buck*, *Kawata* or *Gorsuch*, and *Herbelin*. Applicants therefore respectfully request that the rejection of claim 12 under 35 U.S.C. § 102(b), or in the alternative, under 35 U.S.C. § 103(a), based on *Buck*, *Kawata* or *Gorsuch* in combination with *Herbelin* be withdrawn.

F.   *Buck* or *Kawata* as evidenced by *Deppisch*

The Office rejects claims 2-6 under 35 U.S.C. § 103(a) as obvious over *Buck* or *Kawata* as evidenced by Deppisch et al., Separation and Purification Technology 14:241-254 (1998) ("*Deppisch*"). Office Action, pages 13-14.

Applicants respectfully traverse for the following reasons. Claims 2-6 are dependent from claim 1 and therefore encompass all the elements recited in claim 1. The shortcomings of *Buck* and *Kawata* in anticipating or making obvious the instant invention have already been discussed in previous sections. *Deppisch* does not overcome these shortcomings. In fact, *Deppisch* confirms that the best membranes in the art at the time of the instant invention were recognized to require a sieving coefficient for albumin of below 0.1, thus having a molecular exclusion limit of less than 68 kDa and is silent regarding a membrane having a molecular weight exclusion limit of about 200,000 Daltons, with a sieving coefficient of 0.1 *in water*. *Deppisch* discusses the required properties of membranes used for hemodialysis and hemofiltration:

> A theoretical approach relating membrane structure to transport properties suggests that the deciding factors are pore radius, porosity, tortuosity, diffusion coefficients, pore shape and protein adsorption potential. A hollow fiber structure, which fits these demands for **hemodialysis, hemodialfiltration and hemofiltration**, is a three-layer structure consisting of an inner blood facing skin layer, followed by a sponge structure and a macroporous finger structure.

Deppisch at Abstract.

> This article discusses the **required** membrane properties and relates them to the blood-membrane interaction and hemocompatibility.

Deppisch at page 242, col. 1, 1st ¶ (emphasis added). *Deppisch* singles out the Polyflux S membrane as a membrane that fulfills these requirements the best:

> The demands on membrane structure in extracorporeal blood purification, based on these equations, are as follows. (1) The *pore radius* should have a certain size..... These features considerably determine the morphology and microstructure of modern membranes. The morphological

architecture of some synthetic dialysis membranes, e.g. the
Polyflux S membrane, comes close to fulfilling these
requirements.

Deppisch at page 243, col. 2. *Deppisch* then shows that this state-of-the-art

Polyflux S membrane has a sieving coefficient for albumin of below 0.1 and therefore a

molecular exclusion limit of less than 68 kDa:

> The openness of the membranes is indicated by the sieving
> coefficients for solutes. It is dependent upon the diameter of
> membrane pores and the pore size distribution of the
> membrane. ***The sieving coefficients for a high flux and a
> low flux threelayer Polyflux S membrane measured with
> dextran model solutions is given in Fig. 4.*** The data show
> that the asymmetric high flux Polyflux S membrane has
> sieving coefficients close to the glomerular barrier in the
> human kidney, which is characterized by a high permeability
> for low- and middle-molecular weight substances, and *a
> sharp cut-off minimizing albumin loss*.

Deppisch at page 244, ¶ bridging cols. 1 and 2. The sieving coefficient curves in

Figure 4 demonstrate that the state-of-the-art Polyflux S membrane has a sieving

coefficient for albumin of below 0.1 and therefore a molecular exclusion limit of less than

68 kDa. Therefore, *Deppisch* confirms that the art at the time of the instant invention

recognized a requirement for membranes used in hemodialysis or hemofiltration to have

a molecular exclusion limit of less than 68 kDa and is completely silent regarding a

membrane having a molecular weight exclusion limit of about 200,000 Daltons, with a

sieving coefficient of 0.1 *in water*. *Deppisch* therefore does nothing to overcome the

shortcomings of *Buck* or *Kawata*.

Applicants therefore respectfully request that the rejections under 35 U.S.C.

§ 103(a) based on *Buck* and *Deppisch* or *Kawata* and *Deppisch* be withdrawn.

IV.   Conclusions

In view of the foregoing Remarks, Applicants respectfully request the reconsideration of this application and the timely allowance of the pending claims.
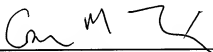
Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: February 12, 2010   By: _____
                                       Carlos M. Tellez
                                       Reg. No. 48,638

Attachments: Figures 3 and 4 missing from U.S. Patent No. 4,935,141 but available
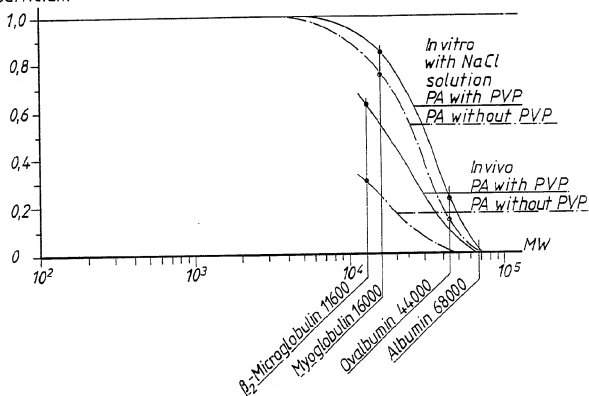from EP 0 305 787.

Fig. 3

Sieving Coefficient

In vitro
with NaCl
solution
PA with PVP
PA without PVP

In vivo
PA with PVP
PA without PVP

MW

10^2 10^3 10^4 10^5

β₂-Microglobulin 11600
Myoglobulin 16000
Ovalbumin 44000
Albumin 68000

Fig. 4

Protein Concentration in Different Rinsing Cycles and Elution Steps

Total Protein Conc. µg/ml

I

II

○ PA(1)= without PVP
× PA(2)= with   PVP

III
Protein Patterns
(Silver stained)

Detectable
○

Slight

Not detectable
○   ○

×   ×   ×

1,1   1,2   1,3
Rinsing without TMP
TBS pH 7,4

2,1   2,2   2,3   2,4
Rinsing with neg.TMP
TBS pH 7,4

2%SDS 2M   2M
1% TRIT.UREA NaCl
Elution